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Increased Prevalence of Cardiovascular and Autoimmune Diseases in Periodontitis Patients: A Cross-Sectional Study

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Background: Associations between periodontitis and cardiovascular and autoimmune diseases are most often assessed in patients with a particular cardiovascular or autoimmune disease. To prevent selection bias, this study assesses the existence of associations between periodontitis and cardiovascular and autoimmune diseases in patients attending a dental or periodontal clinic.

Methods: Data were collected from 1,276 randomly selected dental records from patients attending a dental (n = 588) or periodontal (n = 688) clinic. Data on the prevalence of cardiovascular and autoimmune diseases were obtained from a validated health questionnaire. Data on the presence of periodontitis were taken from patients' dental records.

Results: In uncontrolled analyses, the prevalence of hypertension, diabetes mellitus (DM), and rheumatoid arthritis (RA) is significantly increased in patients with periodontitis. Controlled for confounding, periodontitis was associated with DM, with an odds ratio of 4 (1.03 to 15.3), in the dental clinic. DM was not associated with periodontitis in periodontal clinics. Hypertension does not seem to be associated with periodontitis when controlling for confounders. Periodontitis may be associated with RA in both clinic types.

Conclusions: The increased prevalence of cardiovascular and autoimmune diseases among patients with periodontitis attending dental or periodontal clinics may, at least in part, be influenced by confounding. However, the increased prevalence of DM and RA in patients with periodontitis could not be explained by confounding. *J Periodontol 2010;81:1622-1628.*

KEY WORDS

Arthritis, rheumatoid; diabetes mellitus; periodontitis.

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Periodontitis is a chronic inflammatory disease of the supporting tissues of the teeth. Severe generalized periodontitis affects 5% to 15% of any population worldwide and is a major cause of tooth loss.[1] However, periodontitis seems to affect more than just the supporting tissues of the teeth. Studies have reported associations between periodontitis and cardiovascular and autoimmune diseases,[2-5] such as myocardial infarction,[6,7] hypertension,[8] stroke,[9,10] diabetes mellitus (DM),[11-16] and rheumatoid arthritis (RA).[17-21]

The underlying causes of such associations could be fourfold. First, a disease may predispose to the development of periodontitis. Second, the reverse may be true, periodontitis may predispose to the development of certain diseases. Third, there may be no effect of a disease on periodontitis and no effect of periodontitis on that disease. The association between periodontitis and that disease would then be a coincidental finding caused by a "third" confounding factor. Fourth, periodontitis may indeed cause a certain disease, but only in the presence of a "third" modifying factor. It is also possible that all these mechanisms collectively cause association between periodontitis and a certain disease. Whatever the nature of associations between periodontitis and cardiovascular and autoimmune

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diseases may be, the existence of such associations may be relevant to the prevention of both periodontitis and other diseases.

Because several studies did not find a significant association between periodontitis and cardiovascular or autoimmune diseases,[22-27] the existence of associations among periodontitis and cardiovascular and autoimmune diseases is still not proved beyond doubt. Furthermore, studies that did find a significant association most often assessed periodontal status within groups of patients with a particular cardiovascular or autoimmune disease. Selecting groups of patients with a particular cardiovascular or autoimmune disease may lead to selection bias. The selected patients may not be representative for all patients with a cardiovascular or autoimmune disease, nor of patients attending a dental or periodontal clinic. Therefore, it is unknown whether associations between periodontitis and cardiovascular and autoimmune diseases exist in patients attending a dental or periodontal clinic. The aim of this study is to assess the existence of associations between periodontitis and cardiovascular and autoimmune diseases in a random selection of dental records of patients attending a dental or periodontal clinic.

MATERIALS AND METHODS

Subjects

Data were collected from a convenient sample of 1,276 randomly selected dental records, 588 patients attending a dental clinic and 688 patients attending two periodontal clinics. Selection was performed by randomly picking letters and including all patients whose family name started with the randomly selected letters.

The dental clinic was located in the northern part of The Netherlands (Leeuwarden). Patients attended this clinic for regular dental check-ups once or twice a year. The periodontal clinics were located in the northern (Groningen) and western (Amsterdam) part of The Netherlands, respectively. These periodontal clinics treated patients who were referred for specialist periodontal care.

All patients attending the dental clinic were routinely screened for periodontitis using a Community Periodontal Index of Treatment Needs (CPITN)–based scoring system[28,29] in which probing depths (PDs) were measured on six sites per tooth, on all teeth, and the highest CPITN score per sextant was recorded. If all CPITN scores were <3 in all sextants, indicating no PD ≥4 mm (defined as health to gingivitis), only CPITN scores per sextant were recorded. If any CPITN score was ≥3, indicating PD ≥4 mm (defined as periodontitis), all PD measurements, full mouth at six sites per tooth, were recorded. All patients attending the specialist periodontal clinics underwent full-mouth PD measurements on six sites per tooth, all of which were recorded. Hence, full-mouth PD data were available for all patients with periodontitis. These data were used to calculate the number of sites affected by PD ≥4 mm as a percentage of the total amount of probed sites (extent) and the mean PD (severity).

All patients in dental and periodontal clinics completed the same, extensively validated, self-reported health questionnaire.[30-32] Patients' responses to this questionnaire have previously been compared with the results of a verbal history, taken by an experienced physician (the gold standard). The sensitivity, specificity, and Cohen κ of the medical questionnaire were shown to be 0.88, 0.98, and 0.87, respectively.[33] Information on the prevalence of cardiovascular and autoimmune diseases was obtained from this questionnaire. Additionally, use of medication was also available from the same health questionnaire. This information was used to verify patients' answers regarding the presence or absence of cardiovascular or autoimmune diseases. Information on age, sex, and smoking status was obtained from patients' dental records.

Inclusion Criteria

Records were included of dentate patients who were ≥18 years old, who completed the health questionnaire, and of whom a full-mouth CPITN-based screening or full-mouth PD recording was available. When the interval between date of periodontal screening and date of completion of the health questionnaire exceeded 1 year, records were excluded. This study was approved by the Medical Ethics Committee of the University Medical Center Groningen.

Selection of Other Diseases and Possible Confounders

In the current study, cardiovascular (i.e., hypertension, myocardial infarction, and stroke) and autoimmune (i.e., DM, hypothyroidism, and RA) diseases were chosen from the health questionnaire for analysis on the basis of their reported associations with periodontitis.[2-21] The selection of these diseases from the health questionnaire was performed before analysis. As potential confounders in the relationship between periodontitis and cardiovascular and autoimmune diseases, sex, age, and smoking habits were also assessed; these variables were also selected before analysis of their potential association with periodontitis.

Statistical Analyses

Group 1 consisted of controls (subjects attending the dental clinic without periodontitis). Groups 2 and 3 consisted of periodontitis patients attending, respectively, the dental clinic (Group 2) and periodontal clinics (Group 3) (Tables 1 and 2). First, differences in the prevalence of cardiovascular and autoimmune diseases among three groups of patients were compared

Table 1.

Patients' Characteristics

	Group 1: Dental Clinic, Controls 60% (320)	Group 2: Dental Clinic, Periodontitis 40% (217)	Group 3: Periodontal Clinic, Periodontitis (671)	Overall (Groups 1, 2, and 3) *P* Value	Group 1 Versus Group 2 *P* Value	Group 1 Versus Group 3 *P* Value	Group 2 Versus Group 3 *P* Value
Characteristics							
Sex % (n)*†‡ Males	44 (141)	52 (113)	39 (262)	0.003	0.058	0.165	0.001
Sex % (n)*†‡ Females	56 (179)	48 (104)	61 (409)				
Age (years), mean (± SD)§†‖¶‡	33 (± 11)	41 (± 122)	49 (± 11)	<0.001[K]	<0.001	<0.001	<0.001
Smoking % (n)*#†‡	31 (49 of 158)	28 (32 of 113)	40 (270 of 663)	0.018	0.714	0.039	0.026
Periodontal variables							
Number of teeth, mean (± SD)	Unknown	26 (± 5)	26 (± 4)	NA	NA	NA	0.371
% with PD ≥4 mm, median (interquartile range)‡	None	36 (21% to 52%)	49 (30% to 72%)	NA	NA	NA	NA
PD, median (interquartile range)‡	<4 mm	4.9 mm (4.6 to 5.3 mm)	5.2 mm (4.8 to 5.7 mm)	NA	NA	NA	NA

[K] = Kruskal Wallis test; NA = not applicable.
Differences in potential confounders age, sex, and smoking status were compared among all three groups and pairwise.
Additionally, differences among patients with periodontitis from dental and periodontal clinics were tested pairwise.
* Differences in sex distribution and smoking status were analyzed using χ^2 test.
† Statistically significant difference ($P \leq 0.05$) among Groups 1, 2, and 3.
‡ Statistically significant difference (α of 0.05 corrected with Bonferroni-Holm) between Groups 2 and 3.
§ Differences in age were analyzed using *t* test for independent samples.
‖ Statistically significant difference (α of 0.05 corrected with Bonferroni-Holm) between Groups 1 and 2.
¶ Statistically significant difference (α of 0.05 corrected with Bonferroni-Holm) between Groups 1 and 3.
# Data on smoking were available for ≈50% (271 of 537) of patients in the dental clinic.

(Groups 1, 2, and 3). If there was a significant difference among the three groups, pairwise comparisons were made (Group 1 with Group 2 and Group 1 with Group 3). Differences in the prevalence of cardiovascular and autoimmune diseases were tested for significance using the chi-square test. Differences in potential confounders (age, sex, and smoking status) among patients were tested likewise; first overall (Groups 1, 2, and 3), and in case of a significant difference, second pairwise using the chi-square test and independent sample *t* test as appropriate. Additionally, differences in confounders and disease prevalence among patients with periodontitis attending dental or periodontal clinics (Groups 2 and 3) were tested for significance. For all pairwise comparisons, a Bonferroni-Holm correction for multiple statistical tests was used, adjusting the significance level of 0.05 appropriately.

Diseases that were found to be significantly more prevalent among patients with periodontitis in the univariate analyses were further analyzed using logistic regression (method: backward stepwise). On the basis of the outcomes of the logistic regression, the associations were expressed as odds ratios (ORs) while controlling for potential confounding by age, sex, and smoking status. Smoking was entered into the model as 0 for currently not smoking, or 1 for currently smoking. Age was entered as a continuous variable. Effect modifications (i.e., interactions between variables) were explored. Logistic regression analyses were performed separately for patients with periodontitis attending dental and periodontal clinics by selecting, respectively, Groups 1 and 2 and Groups 1 and 3. All statistics were calculated using a statistical software program.[#]

RESULTS

Patients' Characteristics

In the dental clinic, 91% of 588 randomly selected dental records met inclusion criteria (n = 537; Table 1). The remaining 9% of the selected records (n = 51) was excluded mainly because the interval between the date of periodontal screening and the date of completion of the health questionnaire exceeded 1 year. Full-mouth PD recordings were available for 72% (n = 163) of all patients with a CPITN score of ≥3 (n = 225). In the remaining 28% of the patients with a CPITN score ≥3 (n = 62), full-mouth PD recordings were unavailable because of objection to full-mouth screening for financial or other reasons. On average, 36% (median, with interquartile range,

SPSS v15.0, SPSS, Chicago, IL.

Table 2.

Prevalence of Diseases in Patients With and Without Periodontitis, Without Controlling for Confounding

Disease	Group 1: Dental Clinic, Controls (320)	Group 2: Dental Clinic, Periodontitis (217)	Group 3: Periodontal Clinic, Periodontitis (671)	Overall (Groups 1, 2, and 3) *P* Value	Group 1 Versus Group 2 *P* Vaule	Group 1 Versus Group 3 *P* Value
Hypertension %(n)*†‡	5 (16)	13.4 (29)	16.5 (111)	<0.001	0.001	<0.001
Myocardial infarction %(n)	0.9 (3)	1.4 (3)	2.4 (16)	0.235		
Stroke %(n)	0.3 (1)	2.8 (6)	1.3 (9)	0.058		
Diabetes %(n)*‡	1.6 (5)	5.5 (12)	5.1 (34)	0.023	0.012	0.008
Hypothyroidism %(n)	2.5 (8)	3.2 (7)	4.6 (31)	0.223		
Rheumatoid arthritis %(n)*‡	0.3 (1)	2.8 (6)	3 (20)	0.025	0.021[F]	0.004[F]

Prevalence of cardiovascular and autoimmune diseases is presented as percentages (and numbers) of the total amount of patients in each group. Differences in cardiovascular and autoimmune disease prevalence were compared among all three groups and pairwise (differences between Groups 2 and 3 are not shown; none of these differences was significant).
[F] = calculated using Fisher exact test (expected cell count of <5 in >25% of all cells).
* Statistically significant difference ($P \leq 0.05$) among Groups 1, 2, and 3.
† Statistically significant difference (α of 0.05 corrected with Bonferroni-Holm) in disease prevalence between Groups 1 and 2.
‡ Statistically significant difference (α of 0.05 corrected with Bonferroni-Holm) in disease prevalence between Groups 1 and 3.

21% to 52%) of all probed sites of patients with periodontitis in the dental clinic were affected by median PD of 4.9 mm (interquartile range, 4.6 to 5.3 mm).

In the specialist periodontal clinics, 98% of 688 randomly selected records met the inclusion criteria (n = 671). On average, 49% (median, with interquartile range, 30% to 72%) of all probed sites of patients with periodontitis in periodontal clinics were affected by median PD of 5.2 mm (interquartile range, 4.8 to 5.7 mm). Table 1 shows patients' characteristics.

Results of Univariate, Unadjusted Analyses

The prevalence of periodontitis in the dental clinic was 40% (Table 1; Group 2). Among Groups 1, 2, and 3, age and sex differed significantly (*P* values, respectively, <0.001 and 0.003). Patients with periodontitis in the dental clinic (Group 2) were significantly older than controls (Group 1; mean difference 8 years; $P<0.001$). Patients with periodontitis in the periodontal clinics (Group 3) were on average 16 years older than patients without periodontitis in the control group ($P<0.001$). Periodontitis patients from periodontal clinics were more often female (61% versus 48%; $P<0.001$), and were on average 8 years older ($P<0.008$) than patients with periodontitis in the dental clinic. Data on smoking habits were available for 50% of patients attending the general dental clinic. In specialist periodontal clinics, data on smoking status were present in 99% of cases (663 of 671). Smoking status differed significantly among all groups and between Groups 2 and 3 ($P<0.018$ and $P<0.026$, respectively). Patients with periodontitis from periodontal clinics had significantly more sites affected by significantly deeper PD ($P<0.001$). Prevalence of hypertension, DM, and RA differed significantly ($P<0.001$, $P<0.023$, and $P<0.025$, respectively), among all three groups (Table 2). In the dental clinic the prevalence of hypertension was significantly higher in patients with periodontitis compared to controls ($P = 0.001$). In the periodontal clinics, the prevalence of hypertension, DM, and RA was significantly higher than controls ($P<0.001$, 0.008, and 0.004, respectively). There was no significant difference in the prevalence of any diseases among patients with periodontitis from dental and periodontal clinics (Groups 2 and 3; data not shown).

Results of Logistic Regression Analyses

When controlling for age, sex, and smoking status, periodontitis was the only predictor of DM in the dental clinic with an OR of 4 (1.03 to 15.5, $P = 0.046$).

Periodontitis was kept in the regression models predicting RA presence in both dental and periodontal clinics because the probability for stepwise removal was set at 0.10 (significance of change 0.060 and 0.063 for models of dental and periodontal clinics, respectively). Dental clinic periodontitis was the only predictor that was kept in the model. In periodontal clinics, age and sex were additional predictors of RA. Because only one patient with RA did not have periodontitis (Table 2), of which smoking status was unknown, the ORs (and their confidence intervals) of RA associated with having periodontitis in both models were unrealistically large when controlling for smoking status. Therefore, proper assessment of

the nature of associations between periodontitis and RA could not be performed.

Periodontitis did not predict the presence of the remaining diseases analyzed in this study, i.e. ORs of these diseases were not significantly increased, nor was periodontitis kept in the regression models predicting these diseases.

Introducing age, sex, and smoking status as possible effect modifiers (i.e., instead of introducing them as confounders) did not result in a significantly better regression model nor in significant regression coefficients of these effect modifiers.

DISCUSSION

Most studies on associations among periodontitis and cardiovascular and autoimmune diseases assessed periodontal status within a group of patients with a particular cardiovascular or autoimmune disease. To avoid selection bias, this study assessed these associations in a large random sample of patients attending general dental (n = 537) and periodontal (n = 671) clinics. Several conclusions can be drawn from the results.

In univariate unadjusted analyses, hypertension was significantly more prevalent among periodontitis patients in the dental clinic. DM was almost significantly more prevalent (P <0.012, with significance level P = 0.010 using Bonferroni-Holm correction). Hypertension, DM, and RA were significantly more prevalent among patients with periodontitis in the periodontal clinics. Given the random selection of patients attending these clinics, the increased prevalence of these cardiovascular and autoimmune diseases among patients with periodontitis is probably not the result of selection bias.

When controlling for age, sex, and smoking status as potential confounders, the OR of DM was significantly increased (OR 4; 95% confidence interval, 1.03 to 15.3) in patients with periodontitis in the dental clinic.

The significantly increased prevalence of hypertension among patients with periodontitis may have been the result of confounding by age, sex, and smoking status because no significantly increased ORs were found after controlling for these factors.

Attempts to elucidate the nature of associations between periodontitis and RA, by controlling for the potential confounders of age, sex, and smoking status, were hampered by the low prevalence of RA. When logistic regression analyses were performed controlling for smoking status, periodontitis was kept in the final regression models predicting RA in dental and periodontal clinics. However, results from logistic regression analyses yielded unrealistically large ORs and confidence intervals. Given the low prevalence of RA, a case control study might have been more appropriate to elucidate the nature of associations between periodontitis and RA. However, case control studies are susceptible to selection bias, hence the reason why this study was performed on a random sample of patients attending dental and periodontal clinics. Thus, the nature of the observed association between periodontitis and RA remains unclear, but might be caused by more than just confounding.

The relevance of the significantly increased OR of DM, controlled for confounding, in the dental clinic depends on whether this association can be generalized to the general population and on the nature of this association. Regarding generalization, we did not use a population-based sampling scheme to capture a representative sample of the general population. Rather, a random sample of patients attending a dental clinic was taken from an area where 74% of the general population attends a dental clinic for a yearly check-up.[34] Therefore, our sample might be representative of the general population in the northern part of The Netherlands.

Regarding the nature of the association between DM and periodontitis, there may be a bilateral causal association between periodontitis and DM. On the one hand, DM may lead to periodontitis. Increased levels of blood glucose lead to altered local immune responses, delayed wound healing, and increased chance of infections.[35] On the other hand, periodontitis may lead to DM. An inflammatory burden, consisting of inflammatory mediators, such as tumor necrosis factor-α, interleukin-6, and interleukin-1, in the systemic circulation alters lipid and glucose metabolism[36] and induces insulin resistance.[37-39] This inflammatory burden posed by periodontitis may be quantified by means of the periodontal inflamed surface area.[40] On a group level, an increase in periodontal inflamed surface area has been shown to be associated with an increase in hemoglobinA_{1c} in patients with type 2 DM.[15] Finally, treatment of periodontitis has been shown to improve glycemic control in patients with type 2 DM.[41-48] Therefore, this association could be relevant to public health. However, this study by its nature could not establish causality.

The use of the CPITN to diagnose periodontitis in the dental clinic may be considered a weakness of this study. However, full-mouth PD recordings were available for 72% of patients with a CPITN score ≥3. The results of these 72% show that, with an average number of 26 teeth, around which a median of 36% of probed sites exhibited median PD of 4.9 mm, patients with a CPITN score ≥3 may, at least in our study, safely be regarded as having periodontitis.[49]

The use of questionnaires to assess general health might be considered another point of weakness of this study. However, all clinics used the same

validated health assessment questionnaires. Previous studies have shown that this questionnaire had a sensitivity, specificity, and Cohen κ of 0.88, 0.98, and 0.87, respectively.[33] Thus, the questionnaire applied in this study may be considered a sound indicator of the presence of cardiovascular and autoimmune diseases.

A weakness of this study is that smoking status was available for only 50% of patients attending the dental clinic. Fortunately, there is no reason to assume any form of bias in the availability of data on smoking status because data on smoking status were available in approximately 50% of both patients with periodontitis and healthy controls. However, binary logistic regression analyses controlling for smoking status (and age and sex) could only make use of those patients whose smoking status was known. Thus, sample size was reduced by 50%, thereby decreasing statistical power. This may have hampered analyzing the associations between periodontitis and diseases with a low prevalence. Furthermore, we could not control for smoking duration and dose (pack years).

A final weakness of this study may be that the data originally entered into the dental records were recorded by different professionals, and these professionals were not formally calibrated among the participating clinics. However, all clinicians were highly experienced periodontists, except the one general dentist who collected data in the dental clinic. However, she was trained by the same periodontists who collected the data in periodontal clinics. Therefore, the lack of formal calibration has probably not harmed the validity of our results.

CONCLUSIONS

There is an increased prevalence of cardiovascular and autoimmune diseases among patients with periodontitis attending dental or periodontal clinics. The increased prevalence of DM and RA in patients with periodontitis could not be explained by confounding. The increased prevalence of other diseases is, at least in part, caused by confounding. Nevertheless, these findings might be relevant in safeguarding oral health because these diseases may be regarded as risk indicators of periodontitis.

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REFERENCES

1. Burt B; Research, Science and Therapy Committee of the American Academy of Periodontology. Position paper: Epidemiology of periodontal diseases. *J Periodontol* 2005;76:1406-1419.
2. Lagervall M, Jansson L. Relationship between tooth loss/probing depth and systemic disorders in periodontal patients. *Swed Dent J* 2007;31:1-9.
3. Feitosa DS, Marques MR, Casati MZ, Sallum EA, Nociti FH Jr., de Toledo S. The influence of thyroid hormones on periodontitis-related bone loss and tooth-supporting alveolar bone: A histological study in rats. *J Periodontal Res* 2009;44:472-478.
4. Piconi S, Trabattoni D, Luraghi C, et al. Treatment of periodontal disease results in improvements in endothelial dysfunction and reduction of the carotid intima-media thickness. *FASEB J* 2009;23:1196-1204.
5. Tonetti MS. Periodontitis and risk for atherosclerosis: An update on intervention trials. *J Clin Periodontol* 2009;36(Suppl. 10):15-19.
6. Humphrey LL, Fu R, Buckley DI, Freeman M, Helfand M. Periodontal disease and coronary heart disease incidence: A systematic review and meta-analysis. *J Gen Intern Med* 2008;23:2079-2086.
7. Friedewald VE, Kornman KS, Beck JD, et al. The American Journal of Cardiology and Journal of Periodontology editors' consensus: Periodontitis and atherosclerotic cardiovascular disease. *J Periodontol* 2009;80:1021-1032.
8. Franek E, Klamczynska E, Ganowicz E, Blach A, Budlewski T, Gorska R. Association of chronic periodontitis with left ventricular mass and central blood pressure in treated patients with essential hypertension. *Am J Hypertens* 2009;22:203-207.
9. Janket SJ, Baird AE, Chuang SK, Jones JA. Meta-analysis of periodontal disease and risk of coronary heart disease and stroke. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003;95:559-569.
10. Choe H, Kim YH, Park JW, Kim SY, Lee SY, Jee SH. Tooth loss, hypertension and risk for stroke in a Korean population. *Atherosclerosis* 2009;203:550-556.
11. Taylor GW, Burt BA, Becker MP, et al. Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus. *J Periodontol* 1996;67(Suppl. 10):1085-1093.
12. Saremi A, Nelson RG, Tulloch-Reid M, et al. Periodontal disease and mortality in type 2 diabetes. *Diabetes Care* 2005;28:27-32.
13. Chávarry NG, Vettore MV, Sansone C, Sheiham A. The relationship between diabetes mellitus and destructive periodontal disease: A meta-analysis. *Oral Health Prev Dent* 2009;7:107-127.
14. Katagiri S, Nitta H, Nagasawa T, et al. Multi-center intervention study on glycohemoglobin (HbA1c) and serum, high-sensitivity CRP (hs-CRP) after local anti-infectious periodontal treatment in type 2 diabetic patients with periodontal disease. *Diabetes Res Clin Pract* 2009;83:308-315.
15. Nesse W, Linde A, Abbas F, et al. Dose-response relationship between periodontal inflamed surface area and HbA1c in type 2 diabetics. *J Clin Periodontol* 2009;36:295-300.
16. Wang TT, Chen TH, Wang PE, et al. A population-based study on the association between type 2 diabetes and periodontal disease in 12,123 middle-aged

Taiwanese (KCIS No. 21). *J Clin Periodontol* 2009;36: 372-379.
17. Kässer UR, Gleissner C, Dehne F, Michel A, Willershausen-Zönnchen B, Bolten WW. Risk for periodontal disease in patients with longstanding rheumatoid arthritis. *Arthritis Rheum* 1997;40:2248-2251.
18. Gleissner C, Willershausen B, Kaesser U, Bolten WW. The role of risk factors for periodontal disease in patients with rheumatoid arthritis. *Eur J Med Res* 1998;3:387-392.
19. Mercado FB, Marshall RI, Klestov AC, Bartold PM. Relationship between rheumatoid arthritis and periodontitis. *J Periodontol* 2001;72:779-787.
20. de Pablo P, Chapple IL, Buckley CD, Dietrich T. Periodontitis in systemic rheumatic diseases. *Nat Rev Rheumatol* 2009;5:218-224.
21. Dissick A, Redman RS, Jones M, et al. Association of periodontitis with rheumatoid arthritis: A pilot study. *J Periodontol* 2010;81:223-230.
22. Sjöström L, Laurell L, Hugoson A, Håkansson JP. Periodontal conditions in adults with rheumatoid arthritis. *Community Dent Oral Epidemiol* 1989;17:234-236.
23. Pinson M, Hoffman WH, Garnick JJ, Litaker MS. Periodontal disease and type I diabetes mellitus in children and adolescents. *J Clin Periodontol* 1995;22: 118-123.
24. Joshipura KJ, Rimm EB, Douglass CW, Trichopoulos D, Ascherio A, Willett WC. Poor oral health and coronary heart disease. *J Dent Res* 1996;75:1631-1636.
25. Hujoel PP, Drangsholt M, Spiekerman C, DeRouen TA. Periodontal disease and coronary heart disease risk. *JAMA* 2000;284:1406-1410.
26. Howell TH, Ridker PM, Ajani UA, Hennekens CH, Christen WG. Periodontal disease and risk of subsequent cardiovascular disease in U.S. male physicians. *J Am Coll Cardiol* 2001;37:445-450.
27. Tuominen R, Reunanen A, Paunio M, Paunio I, Aromaa A. Oral health indicators poorly predict coronary heart disease deaths. *J Dent Res* 2003;82:713-718.
28. Van Dijk LJ, Spijkervet FK, Tromp JA. *Atlas of Periodontal Diagnosis* (Dutch). Houten/Diegem: Bohn Stafleu Van Loghum; 2001:70.
29. Bassani DG, da Silva CM, Oppermann RV. Validity of the "Community Periodontal Index of Treatment Needs" (CPITN) for population periodontitis screening. *Cad Saude Publica* 2006;22:277-283.
30. de Jong KJ, Borgmeijer-Hoelen A, Abraham-Inpijn L. Validity of a risk-related patient-administered medical questionnaire for dental patients. *Oral Surg Oral Med Oral Pathol* 1991;72:527-533.
31. de Jong KJ, Oosting J, Abraham-Inpijn L. Medical risk classification of dental patients in The Netherlands. *J Public Health Dent* 1993;53:219-222.
32. de Jong KJ, Abraham-Inpijn L. A risk-related patient-administered medical questionnaire for dental practice. *Int Dent J* 1994;44:471-479.
33. de Jong KJ, Abraham-Inpijn L, Vinckier F, Declerck D. The validity of a medical risk-related history for dental patients in Belgium. *Int Dent J* 1997;47:16-20.
34. National Atlas of Public Health. Version 3.20. Yearly Visit to the Dentist. Available at: http://www.rivm.nl/vtv/object_map/o2447n21251.html. Accessed January 9, 2010.
35. International Diabetes Federation. Electronic version of Diabetes Atlas. Available at: http://www.eatlas.idf.org/webdata/docs/Atlas%202003-Summary.pdf. Accessed June 21, 2009.
36. Iacopino AM, Cutler CW. Pathophysiological relationships between periodontitis and systemic disease: Recent concepts involving serum lipids. *J Periodontol* 2000;71:1375-1384.
37. Grunfeld C, Soued M, Adi S, Moser AH, Dinarello CA, Feingold KR. Evidence for two classes of cytokines that stimulate hepatic lipogenesis: Relationships among tumor necrosis factor, interleukin-1 and interferon-alpha. *Endocrinology* 1990;127:46-54.
38. Feingold KR, Grunfeld C. Role of cytokines in inducing hyperlipidemia. *Diabetes* 1992;41(Suppl. 2):97-101.
39. Pickup JC, Mattock MB, Chusney GD, Burt D. NIDDM as a disease of the innate immune system: Association of acute-phase reactants and interleukin-6 with metabolic syndrome X. *Diabetologia* 1997;40:1286-1292.
40. Nesse W, Abbas F, van der Ploeg I, Spijkervet FK, Dijkstra PU, Vissink A. Periodontal inflamed surface area: Quantifying inflammatory burden. *J Clin Periodontol* 2008;35:668-673.
41. Grossi SG, Skrepcinski FB, DeCaro T, et al. Treatment of periodontal disease in diabetics reduces glycated hemoglobin. *J Periodontol* 1997;68:713-719.
42. Iwamoto Y, Nishimura F, Nakagawa M, et al. The effect of antimicrobial periodontal treatment on circulating tumor necrosis factor-alpha and glycated hemoglobin level in patients with type 2 diabetes. *J Periodontol* 2001;72:774-778.
43. Stewart JE, Wager KA, Friedlander AH, Zadeh HH. The effect of periodontal treatment on glycemic control in patients with type 2 diabetes mellitus. *J Clin Periodontol* 2001;28:306-310.
44. Rodrigues DC, Taba MJ, Novaes AB, Souza SL, Grisi MF. Effect of non-surgical periodontal therapy on glycemic control in patients with type 2 diabetes mellitus. *J Periodontol* 2003;74:1361-1367.
45. Kiran M, Arpak N, Unsal E, Erdoğan MF. The effect of improved periodontal health on metabolic control in type 2 diabetes mellitus. *J Clin Periodontol* 2005;32: 266-272.
46. Faria-Almeida R, Navarro A, Bascones A. Clinical and metabolic changes after conventional treatment of type 2 diabetic patients with chronic periodontitis. *J Periodontol* 2006;77:591-598.
47. Navarro-Sanchez AB, Faria-Almeida R, Bascones-Martinez A. Effect of non-surgical periodontal therapy on clinical and immunological response and glycaemic control in type 2 diabetic patients with moderate periodontitis. *J Clin Periodontol* 2007;34:835-843.
48. O'Connell PA, Taba M, Nomizo A, et al. Effects of periodontal therapy on glycemic control and inflammatory markers. *J Periodontol* 2008;79:774-783.
49. Page RC, Eke PI. Case definitions for use in population-based surveillance of periodontitis. *J Periodontol* 2007;78(Suppl. 7):1387-1399.

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